Tris(2-chloroethyl)phosphate

CAS #115-96-8
Swiss CD-1 mice, at 0.0, 175, 350, 700 mg/kg, gavage
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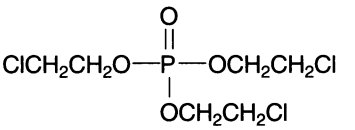

Tris(2-chloroethyl)phosphate (TCEP), used as a flame-retardant for plastics and synthetic fibers, was tested for its effects on reproduction and fertility in Swiss CD-1 mice using the RACB protocol. Preliminary data from a 90-day subchronic toxicity study revealed reproductive effects in B6C3F1 mice; this study was performed as a follow-up to further evaluate the extent and severity of TCEP's reproductive/developmental toxicity. Data from a 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation phase at 175, 350, 700 mg/kg by gavage in corn oil.

In the F_0 animals, two control females, one low dose female, two middle dose males, and one high dose female died during Task 2, for reasons judged not to be related to TCEP exposure (e.g., mate-induced wounds, gavage trauma, septicemia, pneumonia). During Task 2, body weights of treated animals were not different from those of controls.

There were significant effects on reproduction: the number of litters per pair was reduced in the middle and high dose groups by 8 and 63%, respectively. Only 2 of 18 pairs of high dose mice delivered a third litter, compared to 37 of 38 controls. The number of live pups per litter was reduced by 20 and 32% in the middle and high dose groups, respectively, although pup viability, sex ratio, and weight remained unchanged. Cumulative days to deliver each litter was increased in the high dose group only, an effect which started at the second litter (40 days from the start of cohabitation for controls to deliver their second litter versus 66 days for high dose mice).

The last litter from all dose groups was reared by the dam and monitored for viability and growth. There were no pups at the high dose. Although dam weight was reduced by approximately 7% in the middle dose group, compared to control, there were approximately 50% fewer pups per litter, so pup weight gain during nursing was greater in the middle dose group than in controls.

A Task 3 crossover was performed with the controls and high dose animals. In the group mating treated males to control females, just 66% of the pairs mated, and only one female delivered any young. In the treated female × control male group, mating behavior was unaffected, but the number of pups per litter was reduced by approximately 40%.

After this crossover mating, the control and high dose F_0 mice were killed and necropsied. In males, body weight was unchanged, absolute testis weight was reduced by approximately 30%, and relative liver weight and kidney weight was increased by 15% and decreased by 20%, respectively. Epididymal sperm density was reduced by approximately 30%, motility was reduced by greater than 50%, and abnormal forms increased from a control value of 9 to 31%. In high dose treated females, body weight was unchanged and relative kidney weight was reduced by approximately 10%. Antemortem estrous cyclicity was unchanged by TCEP exposure. Microscopically, there were treatment-related increases in hepatocellular degeneration, hepatitis, hepatic cytomegaly, and seminiferous tubular degeneration. Treated females had a greater incidence of renal cytomegaly.

The last litter from the control, low, and middle dose groups provided sufficient mice to evaluate second generation fertility effects. In this mating trial of F_1 adults, the middle dose group had 33% fewer pups per litter, while viability, pup weight, and dam weight were unchanged.

F_1 adults from all remaining groups were killed and necropsied. Middle dose males weighed 6% more than their controls, but there were no other changes seen at or after necropsy. Female body weights did not differ across groups nor were organ weights or estrous cycle parameters different. Microscopically, there were more liver changes in middle dose males than in controls, an effect not seen in females. There were no other significant microscopic lesions.

In summary, these data show clear effects of TCEP on murine reproduction, manifest as fewer litters and smaller litters. At least at the high dose, the effect occurred primarily in the male. In both generations, doses that caused hepatic changes also reduced fertility; whether the converse occurs (fertility changes at doses that do not affect the liver or kidneys) is unknown because of the lack of necropsy data for the F_0 middle dose group.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB92129170**
Chemical: **Tris(2-chloroethyl)phosphate**
CAS#: **115-26-9**
Mode of exposure: **Gavage in corn oil**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	175 mg/kg	350 mg/kg	700 mg/kg
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	—, —
Kidney weight[a]	•	•	↓, ↓
Liver weight[a]	•	•	↑, —
Mortality	—, —	—, —	—, —
Feed consumption	•	•	•
Water consumption	—, —	—, —	—, —
Clinical signs	—, —	—, —	—, —
Reproductive toxicity			
x̄ litters/pair	—	↓	↓
# live pups/litter; pup wt./litter	—	↓, —	↓, —
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight[a]	•	•	↓, —
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	↓, ↓, ↑
Estrous cycle length	•	•	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	—	700 mg/kg

F_1 generation — Dose concentration →	175 mg/kg	350 mg/kg	700 mg/kg
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	↑, ↑	•, •
Mortality	—, —	—, —	•, •
Adult body weight	—, —	↑, —	•
Kidney weight[a]	—, —	—, —	•
Liver weight[a]	—, —	—, —	•
Feed consumption	•	•	•
Water consumption	—, —	—, —	•
Clinical signs	—, —	—, —	•
Reproductive toxicity			
Fertility index	—	—	•
# live pups/litter; pup wt./litter	—, —	↓, —	•
Absolute testis, epididymis weight[a]	—, —	—, —	•
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	•
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, —, —	•
Estrous cycle length	—	—	•

Summary information	
Affected sex?	Both
Study confounders:	None
NOAEL reproductive toxicity:	175 mg/kg
NOAEL general toxicity:	175 mg/kg
F_1 more sensitive than F_0?	Yes
Postnatal toxicity:	No

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.